P24615.A13

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Viswanathan SRINIVASAN et al. **Confirmation No. 4898**
Group Art Unit: 1615

Appl. No: : 10/798,884

Examiner: Sasan, Aradhana

Filed : March 12, 2004

For : DOSAGE FORM CONTAINING A MORPHINE DERIVATIVE AND ANOTHER DRUG

REPLY BRIEF UNDER 37 C.F.R. § 41.41(a)(1)

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, Mail Stop Appeal Brief - Patents
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

This Reply Brief is in response to the Examiner's Answer mailed January 23, 2009, the period for reply extending until March 23, 2009.

In the Examiner's Answer all grounds of rejection set forth in the final rejection are maintained.

Appellants note that the Examiner's Answer does not sufficiently address several of Appellants' arguments as to why the rejections are without merit, and misrepresents some of the facts. These deficiencies have prompted the present Reply Brief.

Appellants also note that this Reply Brief is being filed under 37 C.F.R. § 41.41(a)(1) and is directed to the arguments presented in the Examiner's Answer, and therefore must be entered unless the final rejection is withdrawn in response to the instant Reply Brief.

In order to avoid repetition, the following response to the Examiner's arguments in the Examiner's Answer will be limited to issues which are important enough to warrant a

further comment in Appellants' opinion. Accordingly, Appellants' silence with respect to any allegations set forth in the Examiner's Answer which are not specifically addressed below should by no means be construed as Appellants' admission that these allegations are of any merit.

REPLY

1. Appellants point out again that it is not seen that in view of the passage of Fanara et al., U.S. Patent No. 6,699,502 (hereafter "FANARA") which the Examiner appears to primarily rely on, i.e., col. 2, lines 36-50, one of ordinary skill in the art would have an apparent reason to provide a dosage form which comprises two different active substances, one released immediately after administration and the other one released gradually and regularly after administration, and releases the two active substances in such a manner that the plasma concentration of one active substance is within a therapeutic range over a period which is coextensive with at least about 70 % of the period over which the plasma concentration of the other active substance is within a therapeutic range.

The passage of FANARA primarily relied on by the Examiner makes reference to active substances having "very different pharmacokinetic profiles" which can be administered by means of the immediate/controlled release formulations described therein. FANARA does not explain what is to be understood by the phrase "very different pharmacokinetic profiles". However, according to http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html "pharmacokinetic profile" is a very general and unspecific term which is defined as "[t]he characteristics of a drug that determine its absorption, distribution and elimination in the

body". The Examiner has again failed to explain why one of ordinary skill in the art knowing that the immediate/controlled release combinations set forth in FANARA make it possible to obtain combined therapeutic effects by means of two active substances which have very different characteristics that determine their absorption, distribution and elimination in the body would find it obvious to provide an immediate/controlled release combination according to FANARA for providing plasma concentrations in a therapeutic range of these two active substances in a manner such that the therapeutically effective period of one drug overlaps at least about 70 % of the therapeutically effective period of the other drug. The Examiner has again failed to provide any written (or other) evidence whatsoever which would show that there is an (apparent) link between the different characteristics which determine absorption, distribution and elimination in the body of two drugs and the difference in the duration of action of one of these drugs in relation to the duration of action of the other one of these drugs.

In this regard, it is also pointed out again that there is not a single passage in FANARA wherein the duration of action of any active substance is addressed. Whenever combinations of active substances are mentioned in FANARA these combinations are to be contained in immediate release/controlled release dosage forms, i.e., dosage forms which are designed for the sole purpose of providing different release rates and/or release periods of the active substances, i.e., without any concern regarding the time and duration of action of one active substance in relation to the time and duration of action of the other active substance. This fact alone makes it apparent that FANARA is unable to render obvious the subject matter of any of the present claims.

2. Regarding the graphs at the bottom of page 8 of the Examiner's Answer and the accompanying comments, Appellants note that the Examiner's comments may be an indication that the Examiner has not completely understood the meaning of the rejected claims. At any rate, these (strongly simplified) graphs and the accompanying comments even serve to illustrate the non-obviousness of the subject matter of the rejected claims.

For example, according to graph A ("Co-extensive plasma concentration) there is a measurable plasma concentration for both drugs over the same time period, i.e., from time 0 to time 8. In other words, there is a 100 % overlap in the time periods over which these two drugs show a measurable plasma concentration. However, this overlap does not mean that there also is a 100 % overlap in the periods over which the drugs show plasma concentrations within the therapeutic ranges thereof.

In particular, if one were to assume, for example, that the minimum plasma concentration at which the first drug shows a therapeutic effect is 10, the plasma concentration within the therapeutic range for the first drug would be from time 1 to time 7, i.e., would span 6 time units. If one further were to assume that the minimum plasma concentration at which the second drug shows a therapeutic effect is 15, the plasma concentration within the therapeutic range for the second drug would be from time 2.5 to time 5.5, i.e., would span only 3 time units. Accordingly, despite the fact that both drugs show a 100 % overlap in the time periods over which their plasma concentrations are measurable, in this case the period over which the plasma concentration of the second drug is within the therapeutic range would be coextensive with only 50 % of the period over which the plasma concentration of the first drug is within the therapeutic range.

Accordingly, even if one of ordinary skill in the art were to select suitable formulations for two different drugs to ensure that both drugs, when ingested together, are present in a patient's plasma over substantially the same period, this would by no means guarantee that the periods over which these drugs show plasma concentrations within their therapeutic ranges overlap to a significant extent (as indicated in the rejected claims).

The above remarks should have made it apparent that the concept on which the present invention is based is much more sophisticated than this appears to be appreciated by the Examiner.

3. Regarding Appellants' argument that neither FANARA nor JAEGER (U.S. Patent No. 3,914,425) indicates the plasma half-life of any drug mentioned therein, let alone indicates any difference in the plasma half-lives of two drugs, the Examiner appears to take the position that the mere mentioning of "very different pharmacokinetic profiles" of two drugs in FANARA renders obvious not only the overlap in the periods over which these two drugs show plasma concentrations within the respective therapeutic ranges but also the difference in plasma half-lives which is recited in present claim 72 (see page 18, comments in section 10-c of Examiner's Answer).

Appellants submit that the Examiner's comments in this respect are conclusory and not supported by any evidence whatsoever. Appellants further point out that claim 72 recites, *inter alia*, not only a difference in plasma half-lives but a corresponding difference of at least about 2 about hours.

4. Regarding Appellants arguments with respect to claims 12-14 (and 47) the Examiner alleges in section 10-e at page 19 (and section 10-h at page 22) of the Examiner's Answer that "one with ordinary skill in the art would use the teachings of [FANARA] and [JAEGER] to make a pharmaceutical composition by using drug combinations (antitussives, antihistamines, decongestants, expectorants) with drugs having different plasma half-lives in order to optimize the release of drugs over time. Drugs that are part of the immediate release would have a different plasma half-life than drugs that are part of the controlled release in order to maintain drug release for optimal therapeutic effect."

Appellants submit that also in this case, the Examiner's comments are apparently merely conclusory and not supported by any evidence whatsoever.

It further is pointed out that (dependent) claims 12-14 and 47 recite not only a difference in plasma half-lives but a corresponding difference of at least 2 about hours (see claim 12) or even longer (claims 13 and 14), or at least about 1 hour with respect to the plasma half-lives of codeine, hydrocodeine or hydrocodone (claim 47). Appellants submit that the Examiner has not shown that by following the teaching of FANARA and JAEGER one of ordinary skill in the art would automatically arrive at the recited differences in plasma half-lives (as appears to be alleged by the Examiner), let alone explained why these differences are rendered obvious to one of ordinary skill in the art.

CONCLUSION

The request to reverse the rejection of claims 1-21, 23-52, 72-78, 80-87, 92-96 and 99-116 and to return the application to the Examining Group for prompt allowance is respectfully maintained.

Although no fee is believed to be required for entry of this Reply Brief, the Patent and Trademark Office is hereby authorized to charge any fee that is deemed to be necessary to Deposit Account No. 19-0089.

Respectfully submitted,
Viswanathan SRINIVASAN et al.

Stephen M. Roylance
Reg. No. 31,296

March 17, 2009
GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191